

## Prognostic Significance of Ventricular Arrhythmia After Repair of Tetralogy of Fallot: A 12-Year Prospective Study

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**Objectives.** The aim of this study was to examine the prognostic significance of ventricular arrhythmia on the ambulatory electrocardiogram (ECG) after repair of tetralogy of Fallot.

**Background.** Ventricular arrhythmia is common after repair of tetralogy of Fallot and has been proposed as the basis for late sudden death. The prognostic significance of ventricular arrhythmia on ambulatory ECG and the indications for therapy are uncertain.

**Methods.** We performed a 48-h ambulatory ECG in 86 patients (3 to 45 years old [mean age 14 years]) after repair of tetralogy of Fallot. These patients were then followed up prospectively for 12 years.

**Results.** At initial assessment in 1980, 47 patients (55%) had infrequent uniform ventricular extrasystoles (16 patients) or normal cardiac rhythm (31 patients) (Group 1), and 39 patients (45%) had frequent uniform ventricular extrasystoles ( $>36/h$ , 2 patients), complex extrasystole (30 patients) or nonsustained ventricular tachycardia (7 patients) (Group 2). There were no

significant clinical or hemodynamic differences between the groups. In addition, nine patients had supraventricular tachyarrhythmia. Antiarrhythmic therapy was prescribed only for the 10 patients who had symptoms attributable to arrhythmia. There were two sudden deaths in Group 1 (4%) and one nonsudden death in Group 2 (2.5%). The absolute difference in mortality between groups was therefore 1.5% (95% confidence limits -6% to +9%), excluding a clinically significant difference in outcome. All but 1 of the 39 patients with complex ventricular arrhythmia are alive and well, including those with elevated ( $\geq 60$  mm Hg) right ventricular pressure.

**Conclusions.** Nonsustained ventricular arrhythmia on ambulatory ECG does not identify patients at high risk for sudden death after repair of tetralogy of Fallot. There does not appear to be any advantage in potentially dangerous long-term antiarrhythmic therapy for asymptomatic postoperative patients.

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Sudden death has been a rare but consistent finding in patients followed up for many years after repair of tetralogy of Fallot (1-5). Since the report by Gillette et al. (6) of ventricular premature contractions on the rest electrocardiogram (ECG) in three of nine patients who died suddenly, these deaths have been attributed to ventricular arrhythmia. Widespread use of ambulatory ECG monitoring has resulted in an increased rate of detection of ventricular arrhythmia, predominantly isolated ventricular extrasystole and nonsustained tachycardia in up to 50% of patients after repair of tetralogy of Fallot, most of whom have been asymptomatic (7-11). Current management strategies for these patients differ widely, ranging from active treatment of all arrhythmias in asymptomatic patients to treatment for symptomatic

patients only (12). A rational approach to this common clinical problem requires identification of which, if any, arrhythmia indicates an increased risk of sudden death and whether successful suppression of arrhythmia reduces this risk. In other clinical situations (e.g., in dilated cardiomyopathy or after myocardial infarction), ventricular arrhythmia suppression as such does not necessarily reduce the risk of late sudden death (13,14).

In 1980 we described the first series of patients who underwent ambulatory ECG monitoring after repair of tetralogy of Fallot and found ventricular arrhythmia in 45% (15). We now report the outcome of these patients who were followed up prospectively for 12 years to assess the prognostic significance of ventricular arrhythmia.

### Methods

**Patients.** We identified 86 consecutive patients (59 men, 27 women) who were seen during a follow-up study at the Hammersmith Hospital. All had undergone repair of tetralogy of Fallot between 1959 and 1978 (1959 to 1964, 35

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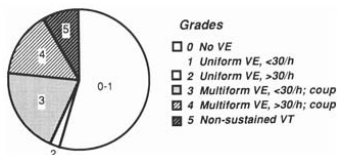
patients; 1963 to 1970, 31 patients; 1971 to 1978, 20 patients) using standard surgical and cardiopulmonary bypass techniques. Of these, 65 patients (76%) had previously undergone palliative surgery (Blalock-Taussig shunt in 53 [61%], Brock procedure in 13 [15%]). The patients all underwent 48-h ambulatory ECG monitoring 4 to 22 years (mean 14 years) after their repair, and approximately half had ventricular arrhythmia. It was decided to confine antiarrhythmic drug therapy to patients who were symptomatic from arrhythmia with palpitations or syncope, or both, so that no asymptomatic patient received prophylactic drug therapy regardless of the grade of arrhythmia. During the following 12 years, this group has been followed up prospectively by clinic visits, telephone calls and questionnaires. All were assessed for a history of palpitations or syncope, documented arrhythmia during follow-up, antiarrhythmic drug therapy and overall clinical status. All 86 patients were followed up until death or 12 years after their initial period of ambulatory ECG monitoring.

**Investigations.** Ambulatory ECG was performed using Oxford Medilog I cassette recorders, bipolar CM, and CM<sub>2</sub> leads and a Reynolds pathfinder high speed analyzer. Ventricular arrhythmias were graded using a modification of the Lown criteria based on frequency and complexity (16): 0 = no ventricular extrasystoles; 1 = uniform ventricular extrasystoles with a peak hourly count <20; 2 =  $\geq 30$  uniform ventricular extrasystoles in any hour; 3 = couplets (two consecutive ventricular extrasystoles) or multiform ventricular extrasystoles with a peak hourly count <30; 4 = couplets or multiform ventricular extrasystoles  $\geq 30$  in any hour; 5 = ventricular tachycardia ( $\geq 3$  consecutive ventricular extrasystoles, mean rate  $>110$  beats/min). In addition, the presence of supraventricular arrhythmia or atrioventricular conduction defect was recorded. Postoperative hemodynamic data were available in 77 (89%) of 86 patients (27 within 24 h of surgery, 50 studied 1 to 23 years [mean 9 years] after operation). At the time of ambulatory ECG monitoring, 39 of the patients (45%) underwent multigated radionuclide angiography using technetium-99m to assess left ventricular function and an ultrashort half-life isotope (krypton-81m, half-life 13 s) for the right ventricle, as described elsewhere (17).

**Statistics.** Descriptive statistics are expressed as mean value  $\pm$  SD. Comparison between groups was performed using an unpaired Student *t* test. Univariate analyses of association were performed using linear regression. Survival curves were constructed using the Kaplan-Meier method, and *p* < 0.05 was statistically significant.

## Results

**Initial evaluation.** On 12-lead ECG in 1980, 84 of the 86 patients were in sinus rhythm, 1 was in atrial fibrillation, and 1 was in ventricular paced rhythm (due to His-Purkinje disease proved at electrophysiologic study). Complete right bundle branch block was present in 81 patients (94%), with



**Figure 1.** Type of ventricular arrhythmia present in 86 patients after repair of tetralogy of Fallot, during 24-h ambulatory electrocardiographic monitoring at baseline. Modified Lown grading was used to classify ventricular arrhythmia (see text). coup = couplets; VE = ventricular extrasystoles; VT = ventricular tachycardia.

left-axis deviation in 12 (14%). During a 48-h ambulatory ECG, 47 patients (55%) had grade 0 to 1 arrhythmia (Group 1) (Fig. 1). The other 39 patients (45%) had ventricular extrasystoles  $\geq$  grade 2 (Group 2), including 7 with nonsustained ventricular tachycardia (3 to 10 beats) of left bundle branch block morphology, consistent with right ventricular or high septal origin. No patient had sustained ventricular tachycardia. In addition, nine patients had supraventricular arrhythmia; five had supraventricular tachycardia; two had paroxysmal atrial fibrillation; and two had frequent atrial extrasystoles ( $\geq 30$ /h). None had second- or third-degree atrioventricular block.

Fifteen patients were symptomatic for arrhythmia. Eleven of 86 patients (13%) complained of palpitations; 5 had ventricular arrhythmia of  $\geq$  grade 2; and 6 had supraventricular arrhythmia. Seven of these patients were treated with antiarrhythmic medications (two with disopyramide, two with digoxin alone, one with digoxin with amiodarone, two with propranolol, according to the individual physician's preference). Four patients (5%) had a history of syncope, all of whom had detailed investigations, including electrophysiologic study. Two of these patients with supraventricular tachycardia were treated with verapamil, and one patient with grade 5 ventricular arrhythmia received sotalol. No arrhythmia could be demonstrated or induced in the fourth patient who was therefore not treated. Syncope has not occurred in any of these patients. No asymptomatic patients received antiarrhythmic therapy, irrespective of the grade of ventricular arrhythmia.

There were no significant differences between the clinical and hemodynamic characteristics of the groups (Table 1). Right ventricular pressure was  $\geq 60$  mm Hg in 23 (30%) of 77 patients. Only one patient had evidence of a residual left to right shunt (pulmonary/systemic flow ratio 1.6), and none had pulmonary hypertension. There was no significant association between right ventricular pressure and ventricular arrhythmia grade (Fig. 2). Right ventricular ejection fraction was below normal (39% to 61% in our laboratory) in 14 of 39 patients (ejection fraction 19% to 38%). Left ventricular ejection fraction was below normal (52% to 71% in our laboratory) in 11 of 39 patients (ejection fraction 26% to

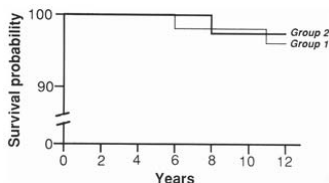
**Table 1. Clinical and Hemodynamic Characteristics of Groups 1 (ventricular arrhythmia grade 0 to 1) and 2 (ventricular arrhythmia  $\geq$  grade 2)**

|                       | Group 1<br>(n = 47)* | Group 2<br>(n = 39)* |
|-----------------------|----------------------|----------------------|
| Age at surgery (yr)   | 12 $\pm$ 8           | 15 $\pm$ 9           |
| Years post-op at AM   | 14 $\pm$ 8           | 15 $\pm$ 7           |
| Age in 1992 (yr)      | 33 $\pm$ 10          | 36 $\pm$ 12          |
| Male/female           | 32/15                | 27/12                |
| Previous shunt        | 29 (62%)             | 24 (62%)             |
| Symptomatic           | 8 (17%)              | 7 (18%)              |
| Antiarrhythmic drugs  | 5 (11%)              | 5 (13%)              |
| Post-op RVSP (mm Hg)† | 35 $\pm$ 23          | 51 $\pm$ 19          |
| RVSP $\geq$ 60 mm Hg  | 13 (32%)             | 10 (26%)             |
| PAP $<$ 30 mm Hg      | 47 (100%)            | 39 (100%)            |

\*For all comparisons between Groups 1 and 2, there were no significant differences ( $p > 0.10$  for all variables). †Postoperative hemodynamic data were available in 41 (87%) of 47 patients in Group 1 and 36 (92%) of 39 patients in Group 2. Values presented are mean value  $\pm$  SD or number (%). AM = ambulatory monitoring; PAP = pulmonary artery pressure; post-op = postoperative; RVSP = right ventricular systolic pressure.

50%). Neither right nor left ventricular ejection fraction was correlated with ventricular arrhythmia grade.

**Follow-up data.** Three patients died during follow-up study; two deaths were sudden and unexpected (Fig. 3). Both sudden deaths were in Group 1 patients with no significant documented arrhythmia during ambulatory ECG. One patient was asymptomatic and received no antiarrhythmic medication. His right ventricular systolic pressure measured 11 years before death had been 90 mm Hg compared with a left ventricular pressure of 110 mm Hg. The second patient had developed occasional palpitations that were due to supraventricular arrhythmia and had been treated with digoxin. His right ventricular pressure had been 60 mm Hg (half systemic). The third patient died of refractory heart failure secondary to documented viral myocarditis 15 years after operation and 7 years after ambulatory ECG monitoring. He was in Group 2, with grade 4 ventricular arrhythmia but no symptoms. Therefore, the risk of late death was not significantly different between the two groups (4% vs. 2.5%, absolute difference in mortality 1.5%; 95% confidence limits, -6% to +9%). Of the 15 patients who had had symptoms



**Figure 3. Actuarial survival curve plotting survival probability versus years followed up for the two study groups (Group 1, no significant ventricular arrhythmia; Group 2, ventricular arrhythmia  $\geq$  grade 2).**

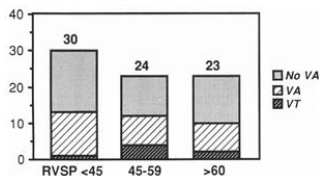
attributable to arrhythmia at initial evaluation (7 of whom were receiving antiarrhythmic medication), all are alive, 12 are asymptomatic, and 3 experience infrequent palpitations only. None have had syncope. Only two patients have developed palpitations during follow-up study. One with supraventricular arrhythmia died suddenly, and the other, who also had supraventricular arrhythmia during ambulatory ECG and had had grade 5 ventricular arrhythmia on initial evaluation, had successful symptomatic relief and arrhythmia suppression with sotalol. Of the 83 survivors, 82 are in New York Heart Association functional class I or II, and 1 is in class III.

## Discussion

In this prospective study with complete follow-up for  $>1,000$  patient-years, nonsustained ventricular arrhythmia during postoperative ambulatory ECG monitoring in patients after repair of tetralogy of Fallot did not identify those who later died suddenly. Asymptomatic patients with high grade ventricular arrhythmia were followed up without antiarrhythmic medication for 12 years, with no late sudden deaths. Furthermore, when symptoms were present, these were due as often to supraventricular as to ventricular arrhythmia. Symptomatic patients with ventricular arrhythmia who received treatment also did well.

**Study limitations.** The study group was not representative of all patients with tetralogy of Fallot for a number of reasons. They represented an early era of surgical management, accounting for their older age at operation and perhaps for the high incidence of ventricular arrhythmia. This high incidence allowed us to examine the prognostic significance of ventricular arrhythmia in a relatively small group. If high grade ventricular arrhythmia had been an adverse prognostic feature, one would have expected a particularly high death rate in our patients because of the high incidence of ventricular arrhythmia and the deliberate decision not to treat any grade of ventricular arrhythmia in the absence of symptoms. There was a mean interval of 15 years between corrective surgery and ambulatory ECG monitoring. This may have

**Figure 2. Relation between right ventricular systolic pressure (RVSP) and ventricular arrhythmia (VA) in the study group. VT = ventricular tachycardia.**



introduced a selection bias if the hazard for sudden death was high in the early postoperative period and decreased thereafter. However, this has not been found in several large retrospective series (2,18,19). In our experience, the incidence of sudden death in the 1st 10 years after surgery was the same as the incidence in the current series (0.3%/patient-year) (11). It is also possible that the incidence of ventricular arrhythmia and sudden death might have increased with an even longer follow-up study, as has been proposed by Garson (12). However, neither our findings in a separate group of patients (18) nor those in other published series demonstrated an increasing hazard for ventricular arrhythmia or sudden death with increasing follow-up study (19-22).

**Ambulatory ECG monitoring.** Ambulatory ECG monitoring was performed at baseline, and the prognostic significance of the findings were assessed for 12 years. This is similar to a clinical situation in which a physician is faced with the decision whether to initiate long-term prophylactic antiarrhythmic treatment on the basis of ventricular arrhythmia over a single period of monitoring. Repeated monitoring would create several subgroups of patients (ventricular arrhythmia followed by no ventricular arrhythmia, the opposite sequence, or consistent findings on serial recordings) whose interpretation would be very difficult because of the natural variability of ventricular arrhythmia using this sampling method (23). Even if some of our patients with no ventricular arrhythmia on initial evaluation had subsequently developed asymptomatic ventricular arrhythmia, this could not have had an adverse prognostic significance because of the excellent outcome of the group as a whole.

Ventricular arrhythmia was common, yet sudden death was rare. The incidence of sudden death in our series (0.3%/patient-year) represents a relative risk of 3 compared with a normal age-matched group. However, the absolute risk of death remains extremely low (approximately half of that for a healthy 50-year old man) (24). Therefore, a better, more specific marker for late sudden death is required instead of a more sensitive technique, such as repeating ambulatory ECG or provocative electrophysiologic studies that might detect even more patients with ventricular arrhythmia. It may be possible to stratify risk by a combination of hemodynamic and detailed electrophysiologic evaluation. In this study, although two of three patients who died had elevated right ventricular pressure, the majority of patients with poor hemodynamic variables (e.g., reduced right or left ventricular ejection fraction or right ventricular systolic hypertension, alone or in combination) remained healthy, even in the presence of high grade ventricular arrhythmia. Before protocols involving more invasive testing can be considered for purposes other than research, prospective data must demonstrate their ability to identify high risk patients.

**Clinical implications.** Patients with symptomatic or sustained arrhythmia, or both, after repair of tetralogy of Fallot need urgent evaluation and therapy; none of our patients who were treated for symptomatic arrhythmia died. How-

ever, the approach to investigation and treatment of asymptomatic patients with high grade, nonsustained ventricular arrhythmia has been controversial. Prophylactic treatment of postoperative arrhythmia has been recommended on the basis of retrospective data (25), but this study did not have control studies for many other potentially confounding variables, such as era or type of surgery. In contrast, another retrospective review showed a low incidence of clinical problems in patients treated for symptoms only despite a high incidence of ventricular arrhythmia (20). This conservative approach is supported by the results of our prospective study.

The concept that suppression of asymptomatic ventricular arrhythmia will necessarily reduce the risk of sudden death has been repudiated by the findings of the Cardiac Arrhythmia Suppression Trial (13). Although this study investigated patients with ischemic rather than congenital heart disease, the results have forced a reappraisal of the role of prophylactic antiarrhythmic therapy for asymptomatic patients with heart disease. In congenital cardiac disease, prophylactic therapy begun in childhood would have to be continued for decades. This might result in important side effects even if the drugs are relatively well tolerated in childhood (26). Furthermore, the risk of sudden death may actually be increased by the administration of potentially proarrhythmic agents. Our findings that asymptomatic patients with ventricular arrhythmia on ambulatory ECG after repair of tetralogy of Fallot are at low risk for late sudden death suggest that antiarrhythmic therapy should be reserved for patients with symptoms attributable to arrhythmia.

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